[Document Name] Claims

1. An aqueous solution preparation containing camptothecins, wherein

the preparation comprises acetic acid and sodium acetate, and

the preparation is at a pH of 2 to 5.

2. The aqueous solution preparation containing camptothecins according to claim 1, wherein the preparation further comprises cyclodextrin.

3. The aqueous solution preparation containing camptothecins according to claim 1 or 2, wherein the camptothecins are 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin.

4. The aqueous solution preparation containing camptothecins according to any one of claims 1 to 3, wherein the aqueous solution preparation is an antitumor preparation.

5. The aqueous solution preparation containing camptothecins according to any one of claims 1 to 4, wherein the aqueous solution preparation is a preparation for injection.

[Document Name] Specification
[Title of the Invention] Aqueous Solution Preparation Containing Camptothecins

[Technical Field]

[0001]

This invention relates to a stable aqueous solution preparation which has excellent solubility for camptothecins.

[Background Art]

[0002]

Camptothecin (CPT) is an alkaloid found in fruits and roots of happy tree (camptotheca acuminata) from China. 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin (CPT-11) (Patent Document 1) which is a semisynthetic derivative of the camptothecin is an important compound since it has the high antitumor activity of the camptothecin simultaneously with reduced toxicity. This 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin is metabolized in the living body to produce 7-ethyl-10-hydroxycamptothecin (SN-38) which is a semisynthetic derivative exhibiting the activity (Patent Document 2).

[0003]

Administration of camptothecins such as 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin is mainly conducted by intravenous injection. Therefore, camptothecins such as 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin are currently commercially available and used as a preparation which has been isotonized with sorbitol or the like. Various attempts have been made to produce preparations of the camptothecins, and exemplary such attempts are a controlled release preparation wherein a camptothecin derivative is incorporated in a copolymer of collagen and 2-hydroxyethyl methacrylate (Patent Document 3) and a controlled release preparation wherein camptothecin or its derivative in a carrier comprising a copolymer of

polylactic acid and glycolic acid copolymer (Patent Document 4).

However, camptothecins exhibit low solubility in water, and heating is required in preparing an aqueous solution preparation, and there is a demand for the development of an aqueous solution preparation containing camptothecins which can be produced in a simplified manner without requiring such heating.

[Patent Document 1] Japanese Patent Publication No. 1991-4077

[Patent Document 2] Japanese Patent Publication No. 1987-47193

[Patent Document 3] Japanese Patent Application Laid-Open No. 1995-277981

[Patent Document 4] Japanese Patent Application Laid-Open No. 1998-17472

[Disclosure of the Invention]

[Problems to Be Solved by the Invention]

[0004]

An object of the present invention is to provide an aqueous solution preparation containing camptothecins which does not require heating in its production, and wherein camptothecins have been solubilized in a stable manner.

[Means for Solving the Problems]

[0005]

In view of the situation as described above, the inventors of the present invention made an intensive study and found that, when acetic acid and sodium acetate are incorporated in the aqueous solution preparation containing the camptothecins, and the aqueous solution preparation is adjusted to a particular pH range, solubility of the camptothecins in the aqueous solution increases, and a stable aqueous solution preparation containing camptothecins having a solubility for camptothecins higher than conventional products can be obtained. The present invention has been completed on the bases of such finding.

[0006]

Accordingly, the present invention provides an aqueous solution preparation containing camptothecins, wherein

the preparation comprises acetic acid and sodium acetate, and

the preparation is at a pH of 2 to 5.

[Merits of the Invention]

[0007]

In the case of the aqueous solution preparation of the present invention, camptothecins can be dissolved at a high concentration without requiring heating in the production process.

[Best Modes for Carrying out the Invention]

[0008]

The camptothecins used in the present invention are the effective component in the aqueous solution preparation of the present invention. Exemplary camptothecins include camptothecins of natural origin such as 10-hydroxycamptothecin, 11-hydroxycamptothecin, 9-methoxycamptothecin, 10-methoxycamptothecin, and 11-methoxycamptothecin; chemically modified natural camptothecins such as 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin (hereinafter sometimes referred as CPT-11). The camptothecin used is preferably CPT-11.

[0009]

The sodium acetate used in the aqueous solution preparation of the present invention may be generated by adding acetic acid and alkaline agent in the aqueous solution preparation. Exemplary alkaline agents used in such case include sodium hydroxide, sodium carbonate, and sodium hydrogencarbonate, and use of sodium hydroxide is preferable. Alternatively, sodium acetate may be generated in the aqueous solution preparation by salt exchange with another compound.

[0010]

The aqueous solution preparation of the present invention preferably contains acetic acid and sodium acetate at a content of 0.1 to 5% by weight, more preferably 0.3 to 3.0% by weight,

and most preferably 0.5 to 2.0% by weight, in terms of acetic acid in view of improving the solubility of camptothecins.

The content of the acetic acid and sodium acetate in terms of acetic acid per 100 mg of the camptothecins in the aqueous solution preparation of the present invention is preferably in the range of 300 to 2000 mg, more preferably 500 to 2000 mg, and most preferably 800 to 1500 mg in view of improving solubility of camptothecins in the aqueous solution preparation.

[0011]

Further incorporation of cyclodextrin in the aqueous solution preparation of the present invention is preferable since such incorporation improves solubility of the camptothecins in the preparation. The cyclodextrin is a irreducible maltooligosaccharide comprising 6 to 12 glucose molecules which have been linked in cycle by α-1,4 glycosidic linkage, and examples include α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, and derivatives thereof. Exemplary cyclodextrin derivatives include maltosyl cyclodextrin, glycosyl cyclodextrin, dimethyl cyclodextrin, and hydroxypropyl cyclodextrin. Preferable examples of the cyclodextrin include β-cyclodextrin, γ-cyclodextrin, and hydroxypropyl β-cyclodextrin.

[0012]

The aqueous solution preparation containing camptothecins of the present invention preferably contains the cyclodextrin at a content of 1 to 20% by weight, and in particular, at 1.5 to 14% by weight in view of improving the solubility of the camptothecins.

In view of improving solubility of camptothecins in the aqueous solution preparation, content of the cyclodextrin per 100 mg of the camptothecins in the aqueous solution preparation of the present invention is preferably in the range of 30 to 1000 mg, and in particular, 90 to 700 mg.

[0013]

The aqueous solution preparation of the present invention is preferably at pH 2 to 5, and more preferably at 2.5 to 4.8

at room temperature (25°C) in view of improving the solubility of camptothecins. The pH is preferably adjusted by using an acid such as acetic acid, hydrochloric acid, and sulfuric acid, or a sodium-containing alkali such as sodium hydroxide, sodium carbonate, and sodium hydrogencarbonate.

[0014]

The aqueous solution preparation of the present invention is useful as an antitumor preparation since the camptothecins which is the effective component has excellent therapeutic effects for malignant tumors. Exemplary applicable malignant tumors include lung cancer, uterine cancer, ovarian cancer, gastric cancer, colorectal cancer, breast cancer, lymphoma, and pancreatic cancer.

[0015]

Preferable dosage form of the aqueous solution preparation of the present invention is preparation for injection, and in particular, preparation for intravenous administration. In preparing such preparation for injection, the preparation may contain in addition to the camptothecins additives such as distilled water for injection, sugars as represented by glucose, mannose, and lactose, inorganic salts as represented by sodium chloride and phosphate, an organic amine such as HEPES and PIPES, and components normally employed in an injection such as stabilizer, excipient, and buffer. The camptothecins is preferably incorporated in the injection preparation at an amount of 1 to 50 mg/mL, and in particular, at an amount of 10 to 30 mg/mL.

[Example]

[0016]

The present invention will be described further in detail with examples; however, it should not be construed that the present invention is limited thereto.

[0017]

Example 1

Acetic acid was added to the aqueous solution shown in Table 1 for pH adjustment, and to 10 mL of this solution was added 250 to 500 mg of CPT-11. The mixture was ultrasonicated for 10 minutes for dispersion and dissolution of the CPT-11 in the aqueous solution, and stirred at room temperature for the period indicated in Table 1. Next, the solution was aliquoted, and centrifuged at 3000 r/min for 30 minutes, and the supernatant was filtered through a 0.45 μm filter. 1 mL of the filtrate was accurately measured, and made up to 50 mL with 90% methanol aqueous solution. The amount of CPT-11 in the solution was measured by HPLC under the conditions as described below.

[0018]

HPLC conditions:

Column: Symmetry Shield RP18 (3.5 μm, 4.6 x 50 mm)

Column temperature: 50°C

Flow rate: 2.0 mL/min

Mobile phase: solution A (50 mmol/L formate buffer (pH 5.5) / acetonitrile / methanol = 850 / 100 / 50) and solution B (50 mmol/L formate buffer (pH 5.5) / acetonitrile / methanol = 750 / 250 / 50). Linear gradient of solution B of 0 to 100% in 15 minutes, followed by 5 minute equilibration with 100% solution A.

Amount injected: 10μL

Detection wavelength: 254nm

[0019]

The measurement results for the amount of CPT-11 in each aqueous solution after stirring for 1 or 2 days at room temperature are shown in Table 1. The results are shown in the amount of CPT-11 in 1 mL of the aqueous solution (CPT-11 in mg/mL).

[0020]

Table 1

	Amount (mg) of the components added per 5 mL of the aqueous solution		pH of the aqueous solution	Period of stirring	
	Sodium acetate	Type of the cyclodextrin		1 day	2 day
Examples of the present invention					
1	100	-	4.0	28.07	20.87
2	100	β 92.5	4.0	29.46	29.13
3	100	γ 336	4.0	31.66	31.52
4	100	γ 672	4.0	30.89	32.09
5	100	Hydroxypropyl β 308	4.0	31.12	31.18
Comparative Examples					
1	Sodium lactate 250 mg		4.0	-	19.03
2	Dimethylacetamide 150 mg		4.2	15.04	14.82
3	Propylene glycol 1500 mg		4.2	15.49	15.49

[0021]

All of the aqueous solution preparations containing camptothecins according to the present invention exhibited excellent solubility for CPT-11. These aqueous solution preparations also exhibited no color change or crystal precipitation when left at room temperature (25°C) for 3 days with no shading. In addition, no precipitation of CPT-11 crystals was noted after shaking of the preparations.

[0022]

Example 2

The following injection preparations 1 to 3 were obtained by the procedure as described below.

To 3.5 mL of the solution having various additives preliminarily dissolved therein was added 100 mg of irinotecan hydrochloride (CPT-11), and the mixture was thoroughly stirred to dissolve the irinotecan hydrochloride. To this solution was added the solution having various additives preliminarily dissolved therein to the total volume of 5 mL.

[0023]

Preparation 1	
Irinotecan hydrochloride	100 mg
Sodium acetate	100 mg
Acetic acid	380 mg
β cyclodextrin	92.5 mg
Water for injection	5 mL in total
pH	4.0

[0024]

Preparation 2	
Irinotecan hydrochloride	100 mg
Acetic acid	380 mg
γ cyclodextrin	672 mg
Water for injection	5 mL in total
pH	4.0

[0025]

The aqueous solution preparations containing camptothecins (injections) of the present invention were pale yellow transparent aqueous solutions, and precipitation of the irinotecan hydrochloride crystals was noted in none of the solutions.

[Document Name] Abstract

[Abstract]

[Objects] To provide an aqueous solution preparation containing camptothecins which does not require heating in its production, and wherein camptothecins have been solubilized in a stable manner.

[Means for Solution] The aqueous solution preparation containing camptothecins contains acetic acid and sodium acetate, and it has a pH of 2 to 5.

[Selected Drawing] None